

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing (day/month/year) 24 AUG 2005	
Applicant's or agent's file reference 14507-45204	
FOR FURTHER ACTION See paragraph 2 below	
International application No. PCT/US04/21387	International filing date (day/month/year) 02 July 2004 (02.07.2004)
Priority date (day/month/year) 02 July 2003 (02.07.2003)	
International Patent Classification (IPC) or both national classification and IPC IPC(7): A61K 31/7076, 31/70 and US Cl.: 514/46, 45, 43; 536/27.6	
Applicant EMORY UNIVERSITY	

1. This opinion contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|--|
| <input checked="" type="checkbox"/> | Box No. I | Basis of the opinion |
| <input type="checkbox"/> | Box No. II | Priority |
| <input type="checkbox"/> | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> | Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> | Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement |
| <input type="checkbox"/> | Box No. VI | Certain documents cited |
| <input type="checkbox"/> | Box No. VII | Certain defects in the international application |
| <input type="checkbox"/> | Box No. VIII | Certain observations on the international application |

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Michael C. Henry Telephone No. 703 308-1235
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Form PCT/ISA/237 (cover sheet) (January 2004)

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International
PCT/US04/21567

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International
PCT/US04/21387

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 6, 18-20, 23-34	YES
	Claims 1-5, 7-17, 21, 22	NO
Inventive step (IS)	Claims 6, 18-20, 23-34	YES
	Claims 1-5, 7-17, 21, 22	NO
Industrial applicability (IA)	Claims 1-34	YES
	Claims NONE	NO

2. Citations and explanations:

Claims 4 and 5 lack novelty under PCT Article 33(2) as being anticipated by POPPENG et al. Claim 4 is drawn to a pharmaceutical composition comprising: (a) a serine protease inhibitor; and (b) adenosine, an adenosine agonist or a pharmaceutically acceptable derivative or prodrug or metabolite thereof. Claim 5 is drawn to the composition of claim 4, involving specific serine protease inhibitors. POPPENG et al. disclose applicant's pharmaceutical composition of claims 4 and 5 which comprises a serine protease inhibitor (aprotinin) and an adenosine derivative (ATP) (see abstract).

Claims 21 and 22 lack novelty under PCT Article 33(2) as being anticipated by GRASSO et al. Claim 21 is drawn to a pharmaceutical composition comprising: (a) a serine protease inhibitor; and (b) an agent that alters activities of G protein coupled receptors and cAMP or a pharmaceutically acceptable derivative or prodrug thereof. Claim 22 is drawn to the composition of claim 21, involving specific serine protease inhibitors. GRASSO et al. disclose applicant's composition of claims 21 and 22 which comprises a serine protease inhibitor (aprotinin) and an agent that alters activities of G protein coupled receptors and cAMP (human FSH or ([125I]-hFSH)) (see abstract).

Claims 6, 18-20 and 23-34 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest a method of treating or preventing ischemia or reperfusion injury comprising administering to a living subject in need thereof a pharmaceutical composition comprising a serine protease inhibitor; and (b) an agent that alters activities of G protein coupled receptors and cAMP or a pharmaceutically acceptable derivative or prodrug thereof, nor suggest a composition comprising a serine protease inhibitor and the claimed adenosine agonists or the claimed agents that alters activities of G protein coupled receptors and cAMP.

Claims 1-3 and 7-17 lack an inventive step under PCT Article 33(3) as being obvious over WEAVER et al. in view of LEE et al. Claims 1-3 and 7-17 are drawn to a method of treating or preventing ischemia or reperfusion injury comprising administering to a living subject in need thereof a pharmaceutical composition comprising a serine protease inhibitor; and (b) adenosine, an adenosine agonist or a pharmaceutically acceptable derivative or prodrug or metabolite thereof. WEAVER et al. disclose a method of treating ischemia or reperfusion injury comprising administering to a living subject (animals) in need thereof a composition comprising a serine protease inhibitor (LEX032) (see abstract). WEAVER et al. also disclose that serine protease inhibitors may reduce ischemia/reperfusion injury (see abstract). However, WEAVER et al. does not use adenosine to treat the same. But, LEE et al. disclose that adenosine can be used to treat ischemic-reperfusion injury (see abstract). This implies that it is obvious to combine any protease inhibitor with adenosine to treat ischemia or reperfusion injury (the same conditions), since both compounds they have the same utility. More specifically, it is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose. *In re Kerkhoven*, 626 F.2d 846, 205 U.S.P.Q. 1069 (C.C.P.A. 1980).

Claims 1-34 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

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NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

- 1 [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
- 2 [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11"
- 3 [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
- 4 [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

L18 ANSWER 3 OF 4

MEDLINE on STN

ACCESSION NUMBER: 87293025 MEDLINE

DOCUMENT NUMBER: PubMed ID: 3303451

TITLE: Assessment of potential therapies for acute T-2 toxicosis in the rat.

AUTHOR: Poppenga R H; Beasley V R; Buck W B

SOURCE: Toxicon : official journal of the International Society on Toxinology, (1987) 25 (5) 537-46.
Journal code: 1307333. ISSN: 0041-0101.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 198709

ENTRY DATE: Entered STN: 19900305

Last Updated on STN: 19900305

Entered Medline: 19870923

AB The efficacy of a variety of approaches for the treatment of animals with acute T-2 toxicosis was assessed utilizing young female rats. A single large dose of the water soluble salt of methylprednisolone significantly prolonged survival times in T-2 toxin treated animals. The use of diltiazem hydrochloride, dazemgrel, N-acetylcysteine, dimethyl sulfoxide, adenosine triphosphate (ATP), ATP combined with magnesium chloride, ascorbic acid, and aprotinin did not prolong survival times at the dosages administered. Trichodermin, a trichothecene similar in structure and biochemical activity to T-2 toxin but much less acutely toxic, had a detrimental effect on survival times whether given 1 hr prior to or after T-2 toxin.

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ACCESSION NUMBER: 1989:471310 CAPLUS

DOCUMENT NUMBER: 111:71310

TITLE: The effects of aprotinin on follicle-stimulating hormone binding and signal transduction in bovine calf testis

AUTHOR(S): Grasso, Patricia; Reichert, Leo E., Jr.

CORPORATE SOURCE: Dep. Biochem., Albany Med. Coll., Albany, NY, 12208, USA

SOURCE: Endocrinology (1989), 125(1), 117-25

CODEN: ENDOAO; ISSN: 0013-7227

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Aprotinin (bovine pancreatic trypsin inhibitor), a serine protease inhibitor, caused a dose-dependent inhibition of ^{125}I -labeled human FSH (^{125}I hFSH) binding to (1) an FSH receptor-enriched light membrane fraction prepared from bovine calf testes homogenates, (2) Triton X-100-solubilized FSH receptor, and (3) proteoliposomes containing incorporated FSH receptor-G-protein-adenylate cyclase (AC) complexes. Equilibrium binding studies with the solubilized receptor indicated that the effect of aprotinin on ^{125}I hFSH binding was due to a decrease in the K_a of the receptor, with no change in FSH-binding capacity. The rate of association of ^{125}I hFSH with its receptor was reduced by 50% in the presence of aprotinin, but no effect on dissociation of FSH-receptor complexes was evident. Aprotinin, at a concentration (250 μM) that inhibited binding of ^{125}I hFSH to the membrane receptor by 25%, completely inhibited basal, fluoride-stimulated and FSH-stimulated AC activity. However, aprotinin, at a concentration (50 μM) that had little effect on ^{125}I hFSH binding, markedly enhanced basal AC activity (3.4-fold) to the level of fluoride and FSH stimulation. Aprotinin did not inhibit $[3\text{H}]5'$ -guanylylimidodiphosphate binding to FSH receptor-enriched membranes, suggesting that its effects on the affinity of the receptor for FSH and on AC activation were not mediated through an interaction with FSH receptor-associated G-protein. No serine protease activity could be detected in the receptor or hormone preps. used in this study. The ability of aprotinin to inhibit binding of ^{125}I hFSH to the Triton X-100-solubilized receptor and to the soluble receptor incorporated into proteoliposomes as well as to the FSH receptor-enriched membrane fraction, all of which are free of serine protease activity, is consistent with the notion that aprotinin may directly interact with the FSH receptor to sterically hinder binding of FSH. Furthermore, the apparent direct effect of aprotinin on basal as well as FSH-stimulated AC activity suggests its general usefulness in studies on the mechanism of signal transduction for ligands thought to operate via the cAMP second messenger system.

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ACCESSION NUMBER: 2002:303480 CAPLUS

DOCUMENT NUMBER: 138:66369

TITLE: LEX032, A Novel Recombinant Serpin, Protects the Brain

AUTHOR(S): after Transient Focal Ischemia

Weaver, Michael; Leshley, Karin; Sands, Howard;

Gritman, Kurt R.; Legos, Jeffrey J.; Tuma, Ronald F.

CORPORATE SOURCE: Department of Physiology, Temple University School of

Medicine, Philadelphia, PA, 19140, USA

SOURCE: Microvascular Research (2002), 63(3), 327-334

CODEN: MIVRA6; ISSN: 0026-2862

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This investigation examined the effectiveness of a serine protease inhibitor (LEX032) when used as a cerebral protective agent after ischemia

. Focal cerebral ischemia in the rat was produced by

intravascular occlusion of the middle cerebral artery for a period of 30

min. Just prior to thread withdrawal (i.e., reperfusion), rats

received an i.v. bolus administration of either vehicle or LEX032 (50

mg/kg), an optimal dose chosen based on previous studies. Somatosensory

evoked potentials (SSEP's) were monitored prior to, during, and for a

period of 60 min after removal of occlusion. The animals were allowed to

recover for 24 h after the ischemic insult. Cortical activity in the

occluded region, as assessed by SSEPs, returned much sooner in the

LEX032-treated animals (10 ± 6 min) than in the untreated animals (40

± 25 min). On a scale ranging from 0 to 3, with three indicating the

most severely injured, the LEX032 animals had a significantly better

neurol. score (1.0 ± 0.9) than the untreated animals (2.3 ± 0.5) 24

h after ischemia. The improved neurobehavior was related to a

55% reduction in brain injury as assessed by TTC staining.

LEX032-treated animals had significantly (P < 0.01) smaller infarcts (115

± 40 mm³) compared to vehicle-treated animals (263 ± 13 mm³). In a

sep. group of animals (n = 6/group), leukocyte infiltration, as evaluated

by tissue myeloperoxidase activity (MPO U/g tissue weight), was also

significantly (P < 0.05) lower in the LEX032-treated animals (1.4 ±

0.3) compared to vehicle-treated animals (3.6 ± 0.7). This data

demonstrates that LEX032 reduces brain injury and suggests that

serine protease inhibitors may reduce

ischemia/reperfusion injury by decreasing

leukocyte activation and migration. (c) 2002 Academic Press.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L15 ANSWER 13 OF 16 MEDLINE on STN
 ACCESSION NUMBER: 2000178187 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 10710542
 TITLE: Protective effects of renal ischemic preconditioning and adenosine pretreatment: role of A(1) and A(3) receptors.
 AUTHOR: Lee H T; Emala C W
 CORPORATE SOURCE: Department of Anesthesiology, College of Physicians and Surgeons, Columbia University, New York, New York 10032, USA.. tl128@columbia.edu
 SOURCE: American journal of physiology. Renal physiology, (2000 Mar) 278 (3) F380-7.
 Journal code: 100901990. ISSN: 0363-6127.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200004
 ENTRY DATE: Entered STN: 20000421
 Last Updated on STN: 20000421
 Entered Medline: 20000410

AB Renal ischemia and reperfusion during aortic and renal transplant surgery result in ischemic-reperfusion injury . Ischemic preconditioning and adenosine infusion before ischemia protect against ischemic-reperfusion injury in cardiac and skeletal muscle, but these protective phenomena have not been demonstrated in the kidney. Rats were randomized to sham operation, 45-min renal ischemia, ischemic preconditioning with four cycles of 8-min renal ischemia and 5-min reperfusion followed by 45-min renal ischemia, systemic adenosine pretreatment before 45-min renal ischemia, or pretreatments with selective adenosine receptor subtype agonists or antagonists before 45-min renal ischemia. Forty-five minutes of renal ischemia followed by 24 h of reperfusion resulted in marked rises in blood urea nitrogen and creatinine. Ischemic preconditioning and adenosine pretreatment protected renal function and improved renal morphology. A(1) adenosine receptor activation mimics and A(1) adenosine antagonism blocks adenosine-induced protection. In addition, A(3) adenosine receptor activation before renal ischemia worsens renal ischemic-reperfusion injury, and A(3) adenosine receptor antagonism protects renal function. We demonstrate for the first time that rat kidneys can be preconditioned to attenuate ischemic-reperfusion injury and adenosine infusion before ischemic insult protects renal function via A(1) adenosine receptor activation. Our data suggest that an A(1) adenosine agonist and A(3) adenosine antagonist may have clinically beneficial implications where renal ischemia is unavoidable.

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COMPOSITIONS AND METHODS FOR USE OF A PROTEASE INHIBITOR AND
ADENOSINE FOR PREVENTING ORGAN ISCHEMIA AND REPERFUSION INJURY

Publication No.: WO/2005/003150

International Application No.: PCT/US2004/021387

Publication Date: January 13, 2005

International Filing Date: July 02, 2004

Priority Data: 60/484,484 July 2, 2003 US

Applicants: EMORY UNIVERSITY

Inventor: VINTEN-JOHANSEN, Jakob

The Novelty:

1. A method of treating or preventing ischemia or reperfusion injury by administering to a living subject in need thereof a pharmaceutical composition comprising: (1) a serine protease inhibitor; and (2) the agents that alter activities of G protein coupled receptors and cAMP, an analog or a pharmaceutically acceptable derivative or prodrug thereof.
2. A pharmaceutical composition, for treating or preventing ischemia or reperfusion injury, comprising: combined use of a serine protease inhibitor and adenosine agonists or the agents that alter activities of G protein coupled receptors and cAMP.

Comments:

1. It becomes obvious by administering a serine protease inhibitor to a living subject for treating ischemia or reperfusion injury in view of WEAVER et al (see abstract).
2. It becomes obvious by administering adenosine to a living subject for treating ischemia or reperfusion injury in view of LEE et al (see abstract).
3. It becomes obvious (Claims 1-3 and 7-17) to combine serine protease inhibitor with adenosine to treat ischemia or reperfusion injury (see the written opinion).
4. What make our claims novelty are the agents that alter activities of G protein coupled receptors and cAMP in combination with serine protease inhibitor and adenosine.
5. After reading the patent application and Written Opinion of the International Searching Authority, we have a strong positive feeling that the major claims will meet the PCT criteria in novelty, inventive step and industrial applicability if we focus on the agents that alter activities of G protein coupled receptors and cAMP in combination with serine protease inhibitor and adenosine.

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